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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 10/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,804	Applicant(s) EISENBACH ET AL.	
	Examiner MISOOK YU, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48 and 52* is/are pending in the application.

4a) Of the above claim(s) *2-14,17,18,35-43 and 46-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,16,19-34,45 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group VI, claims 1, 15, 16, 19-34, 44, 52, in Paper No. 8 is acknowledged. The traversal is on the ground(s) that

1) Mucin in group IV and the elected invention, i.e., peptides derived from Lactadherin belong to the same family of protein.
2) The prior art WO 94 201271 does not teach Lactaherin peptides, therefore DNA encoding Lactaherin peptides and DNA encoding mucin in groups 19 and 20 should be rejoined.
3) Since groups 12 is a method of using the elected product and group 13 is a method of using mucin, they should be also rejoined.
4) Groups 27, and 34 share technical feature of the elected group, and groups 26 and 22 share the technical feature of group IV.

This is not found persuasive because of the reasons set forth in the prior Office Action Paper No. 7, especially page 3 . Further, as for 1)-4) regarding rejoining of mucin, Lactaherin and mucin are two different products with different chemical and molecular structures with different biological activities. Belonging to same family of proteins does not make a same product. As for rejoining of DNA and method of using Lactaherin, the DNA encoding the elected protein and method of using Lactaherin are separate inventions because the first claim of the instant application does not contribute over the prior art. Applicant argue that WO 94 201271 does not teach Lactaherin specifically but the prior art teach other peptides in instant claim 1, therefore the instant claim does not have special technical feature over prior art. Further claim 1 drawn to Lactadherin-derived peptides reads on the protein sequences taught by either US Pat. 5,455,031 (October 3, 1995) or WO 95/15171 (June 8, 1995). Note 102(b) rejection below. Groups 22-28 should include the linking claims 25 and 31, drawn to antigen presenting cells, which is a separate product.

The requirement is still deemed proper and is therefore made FINAL.

However, claim 45 drawn to pharmaceutical composition comprising Lactaherin peptides as main active ingredient and a helper peptide will be rejoined with the elected invention drawn to Lactaherin peptides.

Claims 2-14, 17, 18, 35-43, 46-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-48, 52 are pending and claims 1, 15, 16, 19-34, 45, and 52 are examined as they are drawn to Lactadherin (BA-46) peptides for breast cancer treatment.

Claim Objections

Claims 1, and 52 are objected to because of the following informalities: the claims have not been amended to reflect the elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 15, 16, 19-34, 44, 45, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing for two reasons: First, is "the peptide" comprising 8 to 10 amino acid residues derived from human Lactahderin (BA-46) are 8 to 10 contiguous amino acid of the Lactahderin? Does a peptide comprising residues 100-103 fused to residues 200-203 of the human Lactahderin (BA-46) meet the limitation of claim 1? Second, it is not clear if limitation "of which a second residue from an amino terminal of the peptide and an end residue at a carboxy terminal of the peptide are hydrophobic or hydrophilic natural or non-natural amino acid residues" refers to the peptide comprising the 8 to 10 amino acids or refers to the second and last positions of "8 to 10 amino acids".

Claim 16 recites "the peptide has a sequence selected from the group consisting of SEQ ID NOs: 35-41" but it is not clear what the metes and bounds are for the phrase. Is the peptide consisting of SEQ ID NOs: 35, 36, 37, 38, 39, 40, or 41? Or Does the peptide comprise any of the above sequences? Or does the phrase mean something else? Since the specification at Fig. 13-16 shows data using a peptide consisting of SEQ ID NOs: 35, 36, 37, 38, 39, 40, or 41, this examiner will assume that the claim is drawn to a peptide consisting of SEQ ID NOs: 35, 36, 37, 38, 39, 40, or 41. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claim 20 recites "humanoid" but it is not clear what the metes and bounds are for the term. What is the difference a peptide from human vs. a peptide from "humanoid"?

Claim 23 recites "semipeptoid" but it is not clear what the metes and bounds are for the term.

Claims 24 and 25 are indefinite because claim 25 recites "carrier" and the claim refers to claim 24, which has the limitation "a pharmaceutically acceptable carrier in addition to "at least one peptide" as an active ingredient. However, the species of "a pharmaceutically acceptable carrier" listed in claim 25 is not art accepted "a pharmaceutically acceptable carrier". A pharmaceutically acceptable carrier usually means a buffer suitable for human administration, for example, a buffer without PMSF.

Claim 25 recites the limitation "said at least one tumor associated antigen peptide" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "said at least one tumor associated antigen peptide" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 45 recites "a helper peptide" but it is not clear what the metes and bounds are for the phrase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. The claims are drawn to a Lacthdherin-derived peptide with non-natural modification, which renders the modified peptide more immunogenic or more stable than the unmodified peptide.

The specification teaches:

1) At Figs 1-24, stabilization of RMA-HhD by TAA peptides, CTL activity, characterization of HLA restriction, other than peptides from Lactadherin.
2) Example 3 at pages 38-40 and Fig. 13-17, Lactadherin-derived peptides SEQ ID NOs: 35-41 all binds well to HLA on cell surface at Fig. 13, in vitro CTL activity of SEQ ID NOs: 35-41 are varied at Fig.14, CTL from HhD mice immunized with breast tumor extract peptides induced lysis of cells loaded with SEQ ID NOs: 35-41 at Fig. 15, and 16, and SEQ ID NOs: 35-41 is HLA-A2 restricted at Fig. 17.

However, the instant specification does not teach any a Lacthdherin-derived peptide with non-natural modification, which renders the modified peptide more immunogenic or more stable than the unmodified peptide. What kind(s) of modification is it that renders the modified peptide more immunogenic or stable? Applicant does not describe any modification of the peptide, which renders renders the modified peptide more immunogenic or stable.

Claims 26-29, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. The claims are drawn to a pharmaceutical composition or vaccine comprising an effective amount of a

Lacthdherin-derived peptide to inhibit cancer or cancer metastases. The specification does not teach any Lacthdherin-derived peptide effective to inhibit cancer or cancer metastases. Applicant is requested to point out where in the instant specification teach 1 Lacthdherin-derived peptide effective to inhibit cancer or cancer metastases.

Claims 1, 15, 16, 19-34, 44, 45, and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are as drawn to Lactadherin-derived peptides, and pharmaceutical or vaccine composition comprising a Lacthdherin-derived peptide. Since the specification mostly talks about generating cytotoxic T lymphocytes (CTLs), directed against tumor associated antigen (TAA) derived peptides presented by MHC molecules, the claims are interpreted as drawn to Lactadherin derived-peptides that induce CTLs for treating breast cancer cells. This rejection has several aspects. The instant specification (note its summary 1) and 2) above) does not disclose SEQ ID NOs: 35-41 or any other Lactadherin-derived peptide could be used as antigenic peptide to produce CTLs in vivo or even in vitro. The specification does not provide any direct data that a peptides or any other variants derived from Lactadherin actually produce CTLs that targets any tumor cells. The CTLs in Figures 14-16 are generated with tumor extracts, not by Lactahderin peptides.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that the claimed peptides, pharmaceutical composition comprising the peptides could be used as cancer vaccine or immunogen to generate Lactadherin specific CTLs in vivo. The specification fails to teach in vivo delivery method of the peptides to the target cells for generating the peptide specific CTLs for targeting cancer cells. How is the pharmaceutical whose main ingredient is a peptide delivered into target cells of a mammal? The specification fails to teach how administration of the claimed peptide would produce a sufficient amount of CTLs to kill tumors in an animal or human that has malignant cells expressing Lactahdherin. It is well known in the art that Lactadherin is expressed in normal tissue, i.e. a self-protein

(see page 6 lines 30 and 31 of WO95/15171 and Fig. 5 of Stubbs et al, 1990, Proc. Natl. Acad. Sci. USA 87; 8417-8421), and that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity (Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity.

In addition, one cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or immunogen for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10: 1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: cancer vaccines don't work. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Moreover, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents

to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed peptide in treatment of breast cancer with a reasonable expectation of success.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph rejections, claims 1, 15, 16, 19-34, 44, 45, and 52 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOs: 35-41 being able to complex with HLA-A2, does not reasonably provide enablement for any other Lactahderin-derived peptide fragments capable of specifically being associated with any other MHC molecule. It is not clear if any other Lactaherin-derived peptides other than SEQ ID NO: 35-41could be recognized by any MHC molecule. Furthermore, it is not

clear if (CTLs) could be generated using SEQ ID NO: 35-41 or any other variants either *in vivo or in vitro*, wherein said CTLs specifically target breast cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 15, 19-34, 44, 45, and 52 are drawn to Lachadherin-derived peptides, and pharmaceutical or vaccine comprising the peptides. Since the specification mostly talks about generating cytotoxic T lymphocytes (CTLs), directed against tumor associated antigen (TAA) derived peptides presented by MHC molecules, the claims are interpreted as drawn to Lactadherin derived-peptides that induce CTLs for treating breast cancer cells. The specification discloses at Example 3 at pages 38-40, Figs. 15, and 16 that SEQ ID NOs: 35-41 is being able to complex with HLA-A2 and might be a putative antigenic peptide that could be used to generate HLA-A2 -specific cytotoxic T lymphocytes (CTLs). However, claims 1, 15, 19-34, 44, 45, and 52 encompass any peptide fragment from SEQ ID NO:2 being used as immunogen, wherein said CTLs specifically target breast cells. The specification fails to teach that Lactahderin-derived peptides of claims 1, 15, 19-34, 44, 45, and 52 could be used as an immunogen to stimulate CTLs for targeting breast cancer cells in vivo alone or in combination with any MHC molecule.

One cannot extrapolate the teaching of the specification to invention of claims 1, 15, 19-34, 44, 45, and 52, because there is no guidance on or exemplification of which Lactadherin-derived peptide fragments will be capable of specifically associated with a specific MHC molecule. The specification however does not disclose common structural attributes that identify the claimed peptide fragments that is able to be associate with a MHC molecule. There is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to bind to a MHC molecule. Both Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9 column 1 lines 1-10) and Boon (cited supra, see page 179 column 2, the last paragraph) teaches that antigenic fragment binds to a particular MHC molecule and different MHC molecules bind to different sets of peptides.

Furthermore, it is well known in the art that CTLs recognize and lyse a target cell only in the context of a complex of peptide-MHC class I, which is routed to the cell surface for expression, and potential recognition by specific CTLs, wherein the target cells should have the same subtype of HLA as CTLs (Grey, HM et al, 1994, WO 94/20127, page 1 only). The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict success of the claimed peptide fragment of Lactadherin as an immunogen to induce CTL for killing tumor cells *in vivo* with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 15, 19, 20, 44, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by any of US Pat. 5,455,031 (October 3, 1995), WO 95/15171 (June 8, 1995), or Larocca et el (1991, Cancer Res. 51; 4994-4998).

Claims 1, 15, 19, 20, 44, and 52 are drawn to Lactadherin-derived peptides per se comprising 8-10 amino acids. The instant claims read on the protein sequences disclosed at page 41, Table 2 and the protein sequence at Table 4, page 46 of WO 95/15171. The instant claims also reads on the 46 kDa protein sequence disclosed at Table 2 of columns 27 and 28 of US Pat.5,455,031. The instant claims also reads on the 46 kDa protein sequence disclosed at Figs. 3 and 4 of Larocca et el (1991, Cancer Res. 51; 4994-4998).

Conclusion

Claim 16 is not rejected as obvious over US Pat. 5,455,031 (October 3, 1995) WO 95/15171 (June 8, 1995), and Larocca et el (1991, Cancer Res. 51; 4994-4998) because the references do not teach the peptide consisting of SEQ ID NO:35-41 is HLA-A2-restricted.

No clam is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
October 10, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800 1600